Experimental Neurology 214 (2008) 362–365

Contents lists available at ScienceDirect

Experimental Neurology

journal homepage: www.elsevier.com/locate/yexnr

Short Communication

Transthyretin is not expressed by dorsal root ganglia cells

Mónica Mendes Sousa [a], Maria João Saraiva [b,c,*]

[a] Nerve Regeneration Group, Instituto de Biologia Molecular e Celular- IBMC, Portugal
[b] Molecular Neurobiology Group, Instituto de Biologia Molecular e Celular-IBMC Rua do Campo Alegre 823 4150-180 Porto, Portugal
[c] ICBAS, University of Porto, Portugal

ARTICLE INFO

Article history:
Received 18 July 2008
Revised 12 August 2008
Accepted 21 August 2008
Available online 16 September 2008

Keywords:
Transthyretin
Familial amyloidotic polyneuropathy
Dorsal root ganglia
Amyloid

ABSTRACT

Several mutations in transthyretin (TTR) are related to familial amyloidotic polyneuropathy (FAP), a neurodegenerative disorder caused by extracellular deposition of TTR fibrils, particularly in the peripheral nervous system (PNS). TTR is mainly synthesized by the liver and choroid plexus of the brain that contribute to the plasma and cerebrospinal fluid (CSF) pools of the protein, respectively. It has recently been reported that TTR is additionally expressed in the PNS, namely by peripheral glial cells of dorsal root ganglia (DRG). This lead to the hypothesis that TTR synthesis in the DRG might contribute to the PNS involvement in FAP. In this report we clarify this issue by showing that TTR synthesis is absent in both human and mouse DRG. Moreover, by using TTR KO mouse DRG as controls, we demonstrate that TTR-like immunoreactivity in the perineurium is an artifact. As such, and similarly to what has been previously shown in the central nervous system (CNS), TTR amplification by RT-PCR in the DRG most probably results from contamination by the meninges. In conclusion, TTR deposited in the PNS of FAP patients should still be regarded as having blood and/or CSF origin.

Familial amyloidotic polyneuropathy (FAP) is a lethal neurodegenerative disorder characterized by the extracellular deposition of mutant transthyretin (TTR) aggregates and amyloid fibrils, particularly in the peripheral nervous system (PNS) (Sousa and Saraiva, 2003). TTR amyloid deposits are diffusely distributed in the PNS, involving nerve trunks, plexuses, sensory and autonomic ganglia (Said et al., 1984; Hanyu et al., 1989; Sobue et al., 1990). As a consequence of TTR deposition, axonal degeneration arises, ending up in neuronal loss at ganglionic sites (Dyck and Lambert, 1969; Thomas and King, 1974; Said et al., 1984; Sobue et al., 1990).

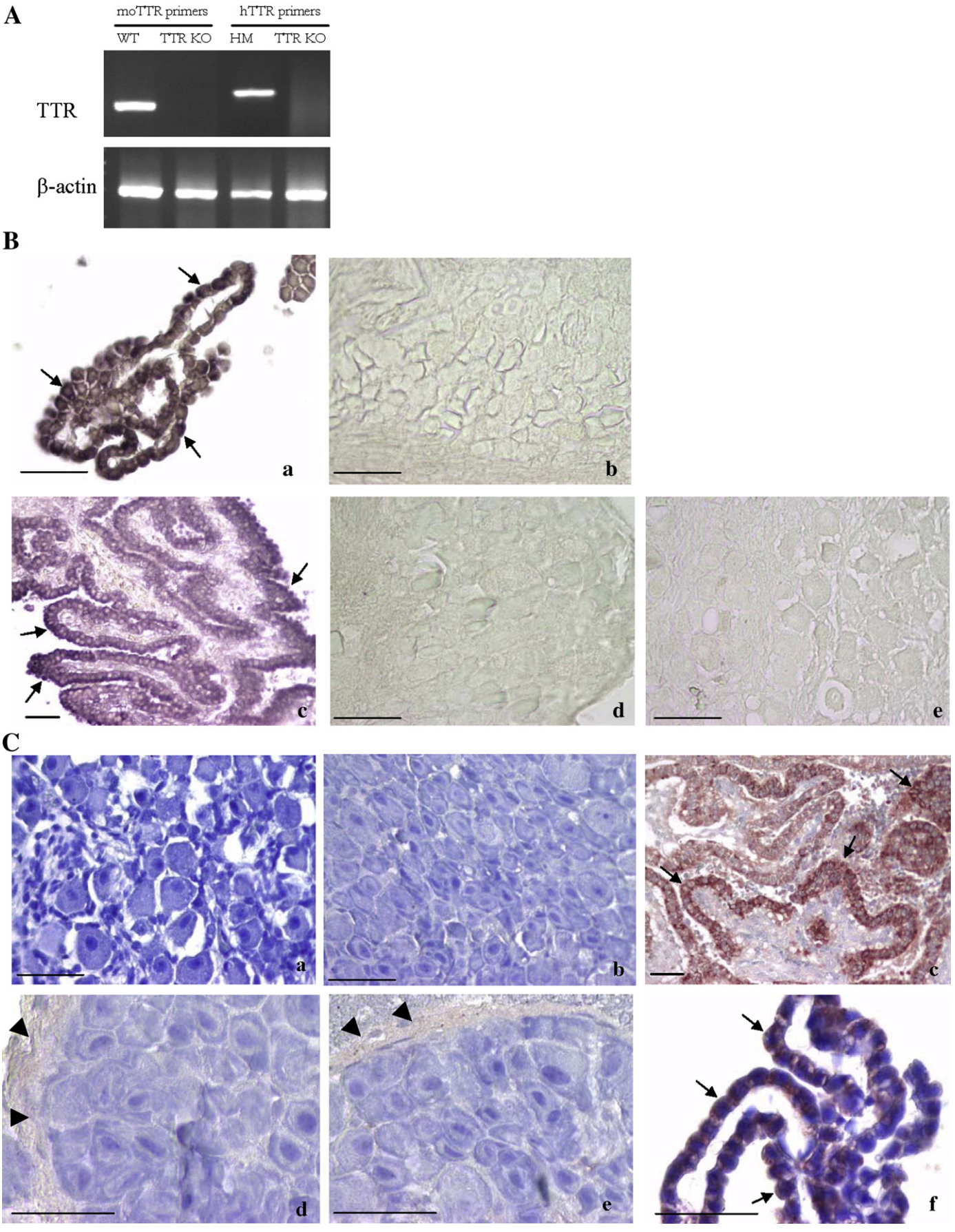
TTR is mainly synthesized by the liver and secreted into the blood (Vatassery et al., 1991). Additionally TTR is actively expressed by the choroid plexus epithelial cells and secreted into the cerebrospinal fluid (CSF) (Aleshire et al., 1983), where it represents approximately 20% of total proteins (Weisner and Roethig, 1983). In the nervous system, besides the choroid plexus, TTR is synthesized in the meninges (Blay et al., 1993). Although a number of studies suggested TTR synthesis in other brain regions, this was shown to be the result of contamination from adjacent choroid plexus cells and meninges (Sousa et al., 2007), confirming that TTR expression is absent in the brain parenchyma. Besides the liver and the choroid plexus, TTR is also expressed by the eye (Cavallaro et al., 1990 and Kawaji et al., 2005), the pancreas (Kato et al., 1985) and in lower levels by the stomach, heart, muscle and spleen (Soprano et al., 1985). During human embryonic development, TTR is synthesized and detected in the fetal blood as early as the eighth week of gestation (Andreoli and Robbins, 1962; Jacobsson, 1989), first in the tela choroidea, the precursor of the choroid plexus, followed by the expression in the liver (Harms et al., 1991; Richardson et al., 1994).

The origin of TTR deposited in the PNS of FAP patients is unknown. TTR has access to the nerve through the blood-nerve barrier and additionally, through contact between peripheral nerve roots and CSF, where TTR is present in high levels. It was recently reported that TTR is expressed in the PNS, by human and rodent glial cells of dorsal root ganglia (DRG) (Murakami et al., 2008). This finding lead the authors to hypothesize that TTR synthesis in the DRG might contribute to the deposition of TTR fibrils particularly in the PNS. Given the novelty of this finding, together with its clinical implications, we further addressed this issue.

As referred to, expression of TTR in human, rat and mouse DRG was recently demonstrated by RT-PCR (Murakami et al., 2008). Based on quantitative RT-PCR analysis, the authors suggested that TTR mRNA expression in human DRG would be about 19- and 33-fold higher than those in the mouse and rat DRG, respectively. To verify this hypothesis, we started by performing RT-PCR for mouse and human TTR using DRG from wild-type (WT) and human TTR transgenic mice in a TTR knockout (KO) background (Kohno et al., 1997), respectively. All animal experiments were conducted in compliance with National rules and with the EC Council Directive 86/609/EEC. In the TTR transgenic mice used, TTR gene expression is driven by the 6-kb upstream region of the human TTR gene (Nagata et al., 1995). As a negative

* Corresponding author. Molecular Neurobiology Group, Instituto de Biologia Molecular e Celular-IBMC Rua do Campo Alegre 823 4150-180 Porto, Portugal. Fax: +351 22 6099157.
E-mail address: mjsaraiv@ibmc.up.pt (M.J. Saraiva).

0014-4886/$ – see front matter © 2008 Elsevier Inc. All rights reserved.
doi:10.1016/j.expneurol.2008.08.019


A
moTTR primers
hTTR primers
WT
TTR KO
HM
TTR KO
TTR
β-actin
B
a
b
c
d
e
C
a
b
c
d
e
f